

SEVENTH ANNUAL SYMPOSIUM ON ANTIBIOTICS*

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The seventh annual Symposium on Antibiotics, organized by the journals *Antibiotics and Chemotherapy* and *Antibiotic Medicine and Clinical Therapy* (Editor, Dr. F. Marti-Ibañez) took place at the Mayflower Hotel, Washington, D.C., U.S.A., on November 3–6, 1959, under the chairmanship of Dr. Henry Welch of the U.S. Food and Drug Administration. Over 800 doctors were registered and 246 papers were presented, 79 of which originated in 22 countries other than the U.S.A. The number of papers scheduled for reading was 160 and two or three rooms were used simultaneously.

Antibiotic Resistance

G. Maurer (*Germany*) demonstrated again that staphylococcal resistance develops and increases during the administration of all antibiotics. In a Burns Unit at the Medical College of Virginia Hospital (150 severely burned patients annually), B. W. Haynes and colleagues, describing wound culture experiments, noted that penicillin, streptomycin, and the tetracyclines approached 100 per cent. ineffectiveness with use. Nasal cultures from unit personnel showed coagulase-positive staphylococci in approximately 25 per cent. throughout the year. Similar rates were noted in the staff of a surgical ward in Washington (W. W. Wright and colleagues) and increasing resistance rates, to both penicillin and tetracycline, were noted in the nasal passages of patients in a rheumatic fever convalescent home in Chicago by M. H. Lepper and associates. The problem of staphylococcal resistance to antibiotics had led to increased investigations of non-antibiotic chemotherapeutic substances such as the nitrofurans and bisquaternary diamines.

Penicillin

W. G. Simpson (*Atlanta*) presented data on penicillin allergic reactions in V.D. patients. In 1954 (19,510 records studied), the reaction rate was 5·9 per 1,000. In 1959 (20,687 records so far studied),

the reaction rate was 9·96 per 1,000. How much of this apparent increase was due to a greater awareness of such reactions was not known.

M. Herold (*Czechoslovakia*) stated that aminopyrine, which had been found to raise the serum levels when given with benzyl penicillin, had failed to do so with phenoxymethyl penicillin (V). Ascorbic acid was remarkably successful in raising the serum levels two-to three-fold.

The first reports were available of the use of potassium alpha-phenoxymethyl penicillin (BL P152), a combination of two diastereoisomeric forms sold commercially in the U.S.A., as "Synicillin" (6-alpha-phenoxymethylpenicillanic acid). Following the work of J. C. Sheehan (*U.S.A.*) who first converted penicillin G to 6-aminopenicillanic acid (and synthesized penicillin V), and that of the English workers Doyle and Rolinson, who found an economic source of this compound in fermentation broths, it was apparent that the synthesis of innumerable new penicillin compounds was now possible. Over 500 had already been prepared by Bristol Laboratories, and, as reported by Dr. Welch in his opening address, by the manipulation of side-chains, broad spectrum, anti-fungal, anti-viral, and anti-tumour penicillins might be future chemical possibilities.

Penicillin P152 had been made chemically by reacting alpha-phenoxymethyl chloride with 6-amino-penicillanic acid obtained from broth. Four papers from the Bristol Laboratories, and two from other sources, reported that in animal protection tests this was consistently more active than penicillin G or V, that it had no irritant properties when administered intradermally, intramuscularly, or even intrathoracically, and that peak serum concentrations after oral administration were substantially higher than with comparable doses of penicillin V. Indeed, the dose-for-dose blood levels obtained with P152 by mouth were similar to those obtained with benzyl penicillin G given intramuscularly.

Moreover, there was some suggestion that the new penicillin was more active than the others against

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certain pathogenic bacteria. It had been shown to be more resistant *in vitro* to *Bacillus cereus* penicillinase than penicillins G or V. Also, in some 762 persons so far treated with P 152, mainly by C. A. Cronk and associates (*Syracuse University*) and by E. M. E. Morigi (*Philadelphia*), only one doubtful case of allergy had been noted. It was postulated that the new penicillin might be attended by a low allergy rate. However, previous penicillin compounds had often been believed to cause a lower rate of allergic reactions only to disappoint when their use had been widened, and caution was required at this stage before any such claim could be advanced. In the United Kingdom the new penicillin was being handled by the Beecham group ("Broxil").

S. Cohen (*Boston*), working with another synthetic penicillin (di-6-benzyl-sulfonamido-penicillanic acid), claimed confirmation that the susceptibility of staphylococci to penicillinase might be significantly lessened by chemical modification of the basic penicillin molecule albeit at the expense of impairment of antibiotic activity.

Streptomycin

If the future position of penicillin was now more secure, that of streptomycin was much less so. The toxic action of streptomycin on the eighth nerve, especially the vestibular apparatus, was well known. The newer dihydrostreptomycin, which had enjoyed widespread use in the U.S.A. on account of its greater stability, had now been shown to be markedly toxic, especially to the cochlear apparatus.

W. H. Harrison (*Chicago*) presented some awe-inspiring audiograms of irreversible, sometimes severe, nerve deafness often occurring several months after even small doses of 1-2 g. dihydrostreptomycin—and in some cases after Kanamycin and Neomycin. Other data were presented by E. W. Christensen (*Lexington, Kentucky*). Dihydrostreptomycin had been mixed with penicillin in a number of preparations used by practitioners. Dr. Welch intervened to announce that the use of dihydrostreptomycin in combination with penicillin had been banned by the U.S. Food and Drug Administration. The only antibiotic with which it could be mixed was streptomycin itself and attention had to be drawn to its toxic effect on the eighth nerve on the label of the package. There was scope for research in Great Britain into the extent of the aural damage which might have been caused by dihydrostreptomycin. As the deafness might not occur until some months had elapsed, the part played by the drug might not always be appreciated.

Reports from Portugal concerned the merthionates of streptomycin and dihydrostreptomycin; it

was suggested that these might be less toxic than the sulphates.

Chloramphenicol

An analogue of chloramphenicol (Dextrosulphenidol) had been tested *in vitro* against the gonococcus by J. D. Thayer and associates (*Chapel Hill, North Carolina*), and compared with Kanamycin, Leucomycin, and chloramphenicol. The new analogue proved to be the most active. It was shown by W. Garson and associates (*North Carolina*) to be 8 to 32 times more effective in experimental syphilis than chloramphenicol. It was suggested that its toxic effects (haemopoietic) might be minimized in man by using much smaller doses.

Tetracycline

This had been used in doses of 1 g. daily for 3 months in cases of chronic bronchitis by P. S. Norman and colleagues (*John Hopkins Hospital, Baltimore*). Benefit was shown in 21 of 39 treatments with tetracycline compared with eleven of 39 treatments with a placebo. J. C. Murdoch (*Royal Infirmary, Edinburgh*) described a double-blind trial in which oxytetracycline (1 g. daily) or dummy tablets were given over a 6-month period for the same condition. Of the forty patients receiving dummies, 27 were off work for 358 days during the winter, whereas 23 of the 26 patients who completed the full course of active treatment remained at work, and the whole series of 35 patients in the treated group were off work for 210 days.

O. De Veiga (*Brazil*) had studied the effect of oxytetracycline on the growth and weight of children. Those receiving 50 mg. daily over a 4-month period increased by 37-41 per cent. in weight and by 37-41 per cent. in height more than the controls.

As with penicillin, a significant advance had occurred with the tetracyclines. The addition of a CH_3 group to penicillin V had increased its absorbability. The deletion of a similar group from chlortetracycline had accomplished a similar improvement. Already a confusing array of tetracycline preparations was on the market. They were based on chlortetracycline, oxytetracycline, and tetracycline itself, with their subsequent potentiation by means of citric acid, the phosphate complex, cosamine, and other means.

A new derivative developed by Lederle, dimethylchlortetracycline (DMCT), was being sold as "Declomycin" within the U.S.A. and Canada and as "Ledermycin" elsewhere. DMCT had been found to produce higher and more persistent blood levels than either chlortetracycline or oxytetracycline, and was excreted only 43 per cent. as fast as tetracycline;

significant serum levels were present 48 to 72 hours longer than after tetracycline. Susceptibility tests on over 850 strains of fifteen bacterial pathogens were reported by M. Finland (*Boston*). The new drug was reported not only to have a similar range to other tetracyclines but also to have proved effective against some strains which were resistant to the tetracyclines. L. P. Garrod (*London*) reported that DMCT was twice as active as tetracycline against some organisms; given to 48 medical students it was well tolerated and the number of bowel actions (1.4 per day) were no more than with other tetracycline preparations.

Many reports were presented concerning its use in pneumonia, brucellosis, urinary tract infections, gonorrhoea, bacillary dysentery, and dermatological conditions. M. Marmell and A. Prigot (*New York*) reported that in gonorrhoea the required dose (600 mg. over 1-2 days) was almost as small as the required dose of tetracycline by injection. All but two of 62 patients were cured. In view of its greater powers it was supplied in capsules of only 125 mg. which might be given two to four times a day instead of the 250 mg. four times a day which was needed for the older established tetracyclines. Side-effects were few in patients treated with 10 mg./kg., but vomiting and nausea occurred in some persons given 15 mg./kg. body weight or more.

Another tetracycline compound described was pyrrolidinomethyl tetracycline. Papers by E. Koch and T. Dimmling (*Germany*) indicated that it had been known in that country since 1957. It was easier to dissolve and was said to be more efficiently absorbed than other tetracyclines when given by injection and less toxic locally. M. A. Kaplan and associates (*U.S.A.*) stated that single daily intragluteal injections of 350 mg. gave serum concentrations which should be adequate for the treatment of most susceptible infections. Single injections of 250 mg. were reported by R. R. Willcox (*London*) to be followed by 30 per cent. of relapses in gonorrhoea, although they were less painful than the same dose of tetracycline phosphate with Lidocaine (Lignocaine), in which 41.2 per cent. of failures were noted. The failures were 16.7 per cent. if a dose of 500 mg. was used. Dr. S. M. Laird (*Manchester*) had 25 per cent. of failures in twenty infections treated with a single injection of 250 mg. but only 8 per cent. if two such injections were given on successive days. The same dose of oxytetracycline (500 mg.) given intramuscularly cured 62 out of 67 cases of gonorrhoea in the hands of E. H. Loughlin (*Haiti*).

Erythromycin

The serum activity of erythromycin propionate

was shown to be greater than that of erythromycin lauryl sulphate. It was well accepted by children with staphylococcal infections and proved effective in gonorrhoea in doses of 500 mg. four times daily for 4 days.

Spiramycin

The complications of scarlet fever were claimed to be controlled with spiramycin by T. Skalmowski (*Poland*).

Oleandomycin

The newer triacetyloleandomycin was shewn to give good results in hospital staphylococcal infections by M. Lefebvre (*Montreal*) and others, in preventing the emergence of resistant organisms in upper respiratory infections in children, and in dermatological conditions. Y. D. Eskelson (*Salt Lake City*) claimed good results in 79 of 85 cases of acne. T. W. Mou (*New York*) had used it for rheumatic fever prophylaxis and concluded that, while penicillin was the antibiotic of choice, triacetyloleandomycin was worthy of further trial in patients allergic to penicillin.

Vancomycin

H. D. Riley (*Oklahoma*) had used Vancomycin in 24 infants and children with severe staphylococcal infections. The results were generally good although several patients expired "of their fundamental disease". A 20 per cent. fatality rate was noted in a similar group treated by R. L. Spears (*Los Angeles*). Vancomycin (0.5-1.0 g. intravenously twice daily for 2-4 weeks) was used for sixteen patients with staphylococcal endocarditis by J. L. Geraci (*Mayo Clinic*) and there were eight deaths. Toxicity was minimal, and manifested itself only by a variable phlebitis.

Ristocetin

L. D. Asay (*Los Angeles*) reported the use of Ristocetin in ninety infants and small children, 57 of whom had serious staphylococcal infections; 82 showed a favourable response, but eosinophilia, neutropenia, thrombophlebitis, and cellulitis were among the side-effects noted. Local complications could be reduced by combining the antibiotic with cortisone.

Kanamycin

This antibiotic was tested in experimental syphilis by T. C. Washburn and associates (*North Carolina*) but the large dose required for cure suggested that it was unlikely to be useful in the human disease. In gonorrhoea, M. Marmell (*New York*) stated that all

of 25 patients were cured with 3 g. given intramuscularly over 3 days, and 54 of 56 with 1.5 g. given over the same time. Other workers reported that 50 per cent. of the blood level of Kanamycin could be found in the bile and 26 per cent. in the pancreatic juice. A specific chronic toxicity of the cochlear nerve was noted in animals.

Antibiotic Combinations

A. M. Torra (*Uruguay*) stated that there was a delay in the emergence of staphylococcal resistance when a combination of tetracycline and oleandomycin was used. After 2½ years use K. Knorr (*Germany*) reported that the resistance figure to *M. pyogenes* was 20 per cent. The combination had been used by M. S. Greif (*Austria*) in the treatment of cholecystitis and negative bile cultures were obtained in 78 out of eighty patients after 4 to 5 days. Other workers reported its successful use in "pneumonopathies", upper respiratory infections in children, serious surgical staphylococcal infections, intestinal amoebiasis, gynaecological infections, and syphilis.

Few data were presented concerning antibiotic/steroid combinations, but J. Kirby and associates (*Washington*) had conducted a controlled blind study of 42 patients with pneumonia; 33.3 per cent. were afebrile 24 hours after therapy when tetracycline alone was used, and 72.2 per cent. when steroids were given in addition.

Anti-Fungal Antibiotics

Systemic fungal disease seemed to be a greater problem in the U.S.A. than in Britain. Amphotericin B had proved life-saving in these serious disorders. G. L. Baum (*Cincinnati*) had used the antibiotic in six cases of histoplasmosis, five of North American blastomycosis, and two of cryptococcosis. One of the histoplasmosis patients died of lung cancer, but the others were well 3 to 18 months after treatment. The antibiotic may produce undesirable and sometimes grave side-effects. C. C. Campbell (*Washington*) noted that, although previously reported as ineffective when given orally, it would prolong the survival time in animals suffering from the above-mentioned diseases when given in the drinking water. It is also active in Leishmaniasis.

A special symposium on Griseofulvin had taken place in Havana a few weeks earlier. This antibiotic was active orally against a variety of fungi associated with dermatophytosis in man and animals. H. Behrman and associates (*New York*) treated 97 children with tinea capitis, and negative cultures were obtained 4 to 13 weeks after therapy. N. J. Goldfarb (*New York*) found griseofulvin of definite

use in the treatment of tinea cruris which responded rapidly, 1 g. daily being the usual dose. It would cause some gastric distress in some patients and instances of psychic stimulation had been reported.

Anti-Tuberculous Drugs

Sulphasoxizole and sulphadimethoxine had proved to be tuberculostatic in guinea-pigs. A new phenyl-PAS and also the use of Cycloserine were described.

Anti-Tumour Antibiotics

Experimental evidence, obtained within the last few years, indicated that certain antibiotics had strong anti-tumour effects on specific animal neoplasms. Studies of these drugs (called "Antimitotics" at a symposium held in Geneva earlier in 1959) might yield information applicable for possible trial against human cancer.

Kanematsu Sugiura (*Sloan-Kettering Institute, New York*) had tested 29 antibiotics against nineteen solid tumours in the mouse, seven in the rat, three in hamsters, three ascites tumours on the mouse, one mouse leukaemia, one mouse virus leukaemia, and one chicken tumour. The first intra-peritoneal injection of the antibiotics at maximum tolerated doses was given 1 to 7 days after tumour transplantation and injections were continued for 7 days. Mitomycin C was possibly the most effective antibiotic tested, and was followed by Fumagillin, 6-diazo-5-oxy-L-norleucine, the actinomycins, actinobolin, sarkomycin, and streptovitacin A.

Mitomycin C, which had been used on 663 malignant cases in 1958 in Japan, was described by Yaemon Shiraha and colleagues (*Osaka, Japan*). Of 194 cases treated, the disease was inoperable in 151 and the 43 others were given Mitomycin C post-operatively to prevent relapse. Three patients with advanced malignancy (maxilla, bladder, stomach) were well 10 to 20 months after starting treatment, as were 24 of 27 cases treated prophylactically. Other work on humans concerned Cyclophosphamide (Cytoxan), which was given to ten children with various types of tumour by H. G. Crambleet (*Iowa*). Remission for 3 to 5 months were noted in two cases of lymphoma, one of rhabdomyosarcoma, and one of Hodgkin's disease, and haematological improvement was noted in two leukaemic patients. Toxic complications included leukopenia and alopecia.

Two new anti-tumour agents—Streptonigrin and the diazomycins—were described. These had been tested by Koppaka Rao and associates (*John L. Smith Memorial Hospital for Cancer Research, New Jersey*). Streptonigrin, prepared from the culture filtrates of *Streptomyces flocculus* was active against adenocarcinoma (755), but only moderately active

against sarcoma (180) and leukaemia (1,210). The diazomycins, which showed a high activity against sarcoma 180 and adenocarcinoma (755) in mice, together with another aliphatic ketone (6-diazo-5-oxy norleucine), formed the active principle of the broth yield of *Streptomyces ambofaciens*.

New Antibiotics

Several new antibiotics were described, perhaps the most promising to date being Colistin, prepared as the sulphate (Colymycin S) or the methanesulphonate (Colymycin M). These were two new forms of the antibiotic obtained by Koyama and associates (Japan) from *Bacillus colistinus*. B. S. Schwartz and others (New Jersey) reported that they were basic polypeptides resembling Polymyxin, although their chemical and pharmacological actions were different. Methanesulphonate was appreciably less toxic in animals than colistin sulphate which might cause stomach ulceration in rats. Neither form was absorbed appreciably from the gastro-intestinal tract.

A. Blaustein (New York) reported no toxicity in man when 76,000—37,500,000 units were given by injection over 5 days; the injections were not painful and the drug had a high degree of activity in infections with *Pseudomonas pyocyaneus*, *E. coli*, *Aerobacter aerogenes*, and other Gram-negative organisms. It was reported as having been successfully used in wound infections and in patients with burns infected with *Pseudomonas aeruginosa*. It had also been successfully used by injection and by mouth in children suffering from gastro-enteritis due to *E. coli*, and fair results had been obtained in cases of *Salmonella* enteritis.

Other new antibiotics included Streptozotocin, prepared from a variant of the soil streptomycete, *Streptomyces achromogenes*, and developed by the Upjohn laboratories. No cross-resistance was noted

with ten other antibiotics now commercially available. Another was Fervenuin, which in animal studies had shown antitrichomonal and anti-tumour activity. It was too early to judge the range of usefulness of these antibiotics in man. A new antibiotic from the Lederle laboratories was Aspartocin, prepared from *Streptomyces griseus*, var. *spiralis*, and stated to be effective against a number of penicillin- and tetracycline-resistant staphylococci. Parke Davis and Co. had introduced Humatin (Paromomycin), a new anti-staphylococcal antibiotic claimed to be useful also in intestinal amoebiasis, which was not yet in production. Four papers from Italy described the use of Rifomycin, which had been used on 27 patients with various infections by S. Furesz (Milan).

Laboratory Methods

In one of a number of papers on antibiotic sensitivity-testing, A. Branch (Canada), having tested penicillin-sensitivity disks from the U.S.A., Canada, and Europe, concluded that there was a pressing need for standardization of methods and interpretation and of disk concentrations, so that a proper exchange of information and understanding could take place on a national and international scale. This plea was echoed by T. G. Anderson (Philadelphia).

The introduction of automation into turbidimetric assays was reported by D. M. Hucke (Pfizer Laboratories, New York). Using two spectrophotometers, a digital voltmeter, and IBM equipment, a system has been developed which automatically recorded light-transmission readings on punch cards, which were fed into the computer in which the test results were calculated, and then returned to the laboratory for reporting.